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MAPPING BY MUTAGENESIS THE DOMAINS OF HUMAN BOWES GALANIN RECEPTOR INVOLVED IN THE INTERACTIONS WITH GALANIN AND CHIMERIC GALANIN RECEPTOR LIGANDS. K. Kask, M. Berthold, U. Kahl, U. Langel, T. Bartfai. Department of Neurochemistry and Neurotoxicology, Stockholm University, S-10691, Sweden.

Molecular cloning of the cDNA for galanin receptor from human Bowes melanoma cell line (Harbert-Ortoli et al., 1994) has made it possible to study which domains or single amino acids on the galanin receptor participate in the interactions with its ligands. To address this question a mutagenesis study using deletions and non-conservative exchanges of amino acids in the extracellular and putative transmembrane regions of the receptor in combination with ligand binding to cells transiently transfected with cDNA constructs was carried out. It appears that changes in the N-terminal extracellular region including the glycosylation sites have no impact on the binding of galanin while substitution of certain amino acids in the transmembrane region VI, in particular His^{264}, completely abolishes the binding of [^{125}I]galanin to transfected 293 cells. This data indicates that the binding of galanin to its receptor most likely does not involve interactions over the large areas in contact, it is rather quite possible that specific strong interactions between single amino acids from both receptor and ligand make the major contribution to the binding free energy needed for high affinity and selectivity.

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EFFECTS OF THE PEPTIDERGIC GALANIN ANTAGONIST, M40, ON GALANIN-INDUCED DEFICITS ON AN OPERANT MEMORY TASK IN RATS. M.P. McDonald, J.N. Crawley. Section on Behavioral Neuropharmacology, NIMH, Bldg. 10 Room 4N214, Bethesda, MD 20892.

Galanin is a 29-amino acid neuropeptide that coexists with acetylcholine (ACh) in the medial septum and diagonal band in the rat, areas that are associated with mnemonic function. Galanin inhibits the release of ACh in the ventral hippocampus, and is overexpressed in the basal forebrain in Alzheimer's disease. Galanin administered in the lateral ventricles or ventral hippocampus of rats significantly impairs choice accuracy on an operant delayed nonmatching to position (DNMTP) task. M40, a peptidergic galanin antagonist (galanin[1-13]-PRO-ALA-LEU-ALA-LEU-ALA-NH_2), blocks galanin-induced feeding without significant motor effects. The current experiment tests the effects of three doses of M40 or vehicle on working memory impairments induced by galanin injected into either the lateral ventricle or the ventral hippocampus. The ability of M40 to antagonize galanin-induced memory deficits is an important preliminary test of the potential usefulness of M40 as a therapeutic agent.